General

Guideline Title

Systemic therapy for well and moderately differentiated unresectable pancreatic neuroendocrine tumours.

Bibliographic Source(s)

Alberta Provincial Endocrine Tumour Team. Systemic therapy for well and moderately differentiated unresectable pancreatic neuroendocrine tumours. Version 2. Edmonton (AB): CancerControl Alberta; 2015 Feb. 18 p. (Clinical practice guideline; no. ENDO-001). [68 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Provincial Endocrine Tumour Team. Targeted therapies for well and moderately differentiated unresectable pancreatic neuroendocrine tumours. Edmonton (Alberta): CancerControl Alberta; 2012 Nov. 16 p. (Clinical practice guideline; no. ENDO-001). [52 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

The choice and sequence of systemic therapy treatment is determined by patient factors, tumour factors, potential therapy related adverse events, and patient preferences, as assessed by the treating oncologist. If available and patient is eligible, consider treatment on a clinical trial or referral to a specialized centre for consideration for radionuclide therapy.

1. Sunitinib malate has been shown to prolong progression free survival (versus placebo) in patients with well differentiated unresectable pancreatic neuroendocrine tumours (PNETs).
    a. Sunitinib malate is recommended for progressive, well and moderately differentiated PNETs in adults with unresectable locally advanced or metastatic disease.
    b. Sunitinib malate should be given at a dose of 37.5 mg, orally, once daily, with or without food, continuously without a scheduled off-treatment period.
2. Everolimus has been shown to prolong progression free survival (versus placebo) in patients with unresectable, well or moderately differentiated PNETs.
    a. Everolimus is recommended for unresectable or metastatic, well or moderately differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease.
    b. Everolimus should be given at a dose of 10 mg, orally, once daily. Treatment should continue as long as clinical benefit is observed or

until unacceptable toxicity occurs.

3. Capecitabine and temozolomide in combination has not been compared to placebo, however, a potential for clinical benefit is suggested from a recently presented phase II study.
    a. Capecitabine and temozolomide in combination is a reasonable option for consideration in treatment of patients with unresectable or metastatic PNETs.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Pancreatic neuroendocrine tumours (PNETs)

Guideline Category

Management

Treatment

Clinical Specialty

Endocrinology

Neurology

Oncology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide evidence-based recommendations on the use of systemic therapies for pancreatic neuroendocrine tumours (PNETs) and to define which patients are acceptable candidates for treatment with the agents

Target Population

Patients diagnosed with well or moderately differentiated (grade 1 or 2) pancreatic neuroendocrine tumours (PNETs)

Interventions and Practices Considered

1. Sunitinib malate
2. Everolimus
3. Capecitabine and temozolomide in combination

Major Outcomes Considered

- Response rate (complete, partial, stable disease)
- Survival rates (5-year, progression-free, overall)
- Adverse events

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Research Questions

Specific research questions to be addressed by the guideline document were formulated by the guideline lead(s) and Knowledge Management (KM) Specialist using the PICO question format (Patient or Population, Intervention, Comparisons, Outcomes).

Guideline Questions

- What is the role of sunitinib malate in the management of patients with pancreatic neuroendocrine tumours (PNETs)? What selection criteria should be considered when identifying patients who are appropriate for treatment with sunitinib malate? What dose and schedule is recommended?
- What is the role of everolimus in the management of patients with PNETs? What selection criteria should be considered when identifying patients who are appropriate for treatment with everolimus? What dose and schedule is recommended?
- What is the role for the combination for capecitabine/temozolomide in the management of patients with PNETs? What selection criteria should be considered when identifying patients who are appropriate for treatment with capecitabine/temozolomide? What dose and schedule is recommended?

Search Strategy

The PubMed database was searched (1965 through 2012 March) for relevant publications using the following search terms: *Sutent* or *sunitinib malate* or *everolimus* AND *pancreatic neuroendocrine*. Results were limited to randomized controlled trials and phase II-III clinical trials. In addition, the National Guideline Clearinghouse (NGC) database was searched (2006 through 2012 March) for existing guidelines and the American Society of Clinical Oncology (ASCO) meeting abstracts database was searched (2009 through 2012 March) for relevant abstracts. Finally, chemotherapy protocols for sunitinib malate and everolimus were searched on the Cancer Care Ontario (CCO) and British Columbia Cancer Agency (BCCA) Web sites.

The search was updated in 2014 to include capecitabine and temozolomide therapy (2012 through 2014 October) and include the MEDLINE and EMBASE databases. A summary of the included literature can be found in Appendix B in the original guideline document.

Inclusion/exclusion criteria: Clinical trials investigating the use of systemic therapy for PNETs.

Number of Source Documents

A total of nine citations were returned from MEDLINE (eight were relevant), and 21 abstracts were selected from American Society of Clinical Oncology (ASCO) for the original guideline. A total of 197 articles were retrieved for the update. Of these, 14 studies were included.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Expert Consensus (Committee)

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Neuroendocrine Tumour Team and a Knowledge Management (KM) Specialist from the Guideline Utilization Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the GURU Handbook (see the "Availability of Companion Documents" field).

Evidence Tables

Evidence tables containing the first author, year of publication, patient group/stage of disease, methodology, and main outcomes of interest are assembled using the studies identified in the literature search. Existing guidelines on the topic are assessed by the KM Specialist using portions of the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument (http://www.agreetrust.org) and those meeting the minimum requirements are included in the evidence document. Due to limited resources, GURU does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required for the reader to judge for himself the quality of the studies.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Development and Revision History

This guideline was reviewed and endorsed by the Alberta Provincial Endocrine Tumour Team. Members of the Alberta Provincial Endocrine Tumour Team include medical oncologists, endocrinologists, surgeons, and nurses. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Neuroendocrine Tumour Team and a Knowledge Management (KM) Specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook (see the "Availability of Companion Documents" field).

The original guideline titled Targeted therapies for well and moderately differentiated unresectable pancreatic neuroendocrine tumours (PNETs) was developed November 2012. This guideline was revised in February 2015.

Formulating Recommendations

The working group members formulated the guideline recommendations based on the evidence synthesized by the KM Specialist during the planning process, blended with expert clinical interpretation of the evidence. As detailed in the Guideline Utilization Resource Unit (GURU) Handbook, the working group members may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution or institutions to better reflect local practices, or develop their own set of recommendations by adapting

some, but not all, recommendations from different guidelines.

The degree to which a recommendation is based on expert opinion of the working group and/or the Provincial Tumour Team members is explicitly stated in the guideline recommendations. Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations, the GURU does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Guideline Review and Approval

When the draft guideline document has been completed, revised, and reviewed by the Knowledge Management (KM) Specialist and the working group members, it is sent to all members of the Provincial Tumour Team for review and comment. This step ensures that those intended to use the guideline have the opportunity to review the document and identify potential difficulties for implementation before the guideline is finalized. Depending on the size of the document, and the number of people it is sent to for review, a deadline of one to two weeks will usually be given to submit any feedback. Ideally, this review will occur prior to the annual Provincial Tumour Team meeting, and a discussion of the proposed edits will take place at the meeting. The working group members will then make final revisions to the document based on the received feedback, as appropriate. Once the guideline is finalized, it will be officially endorsed by the Provincial Tumour Team Lead and the Executive Director of Provincial Tumour Programs.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriately targeted therapies for well and moderately differentiated unresectable pancreatic neuroendocrine tumours (PNETs)

Potential Harms

- In terms of toxicity, the most frequent adverse events (any grade) associated with sunitinib malate are fatigue/asthenia (60% versus 52% placebo), diarrhea (59% versus 39% placebo), and nausea (45% versus 29% placebo). The most frequent grade 3 or 4 events were

neutropenia (12% versus 0% placebo) and hypertension (9.6% versus 1.2% placebo). Patients, especially those with a history of cardiovascular disorders, for whom sunitinib is planned should be monitored closely by physicians for cardiovascular events.
- In terms of toxicity, the most frequent adverse events associated with everolimus alone are stomatitis (64% versus 17% placebo), rash (49% versus 10% placebo), diarrhea (34% versus 10% placebo), fatigue (31% versus 14% placebo), and infections (23% versus 6% placebo). The most common grade 3 or 4 events were anemia (6% versus 0% placebo) and hyperglycemia (5% versus 2% placebo). Patients for whom everolimus is planned should be monitored by physicians for these side effects.

Refer to Table 2 in the original guideline document for the toxicity profiles of sunitinib malate and everolimus.

Refer to Tables 1, 2, and 3 in Appendix B in the original guideline document for a complete listing of adverse events for guideline therapies reported in clinical studies.

Qualifying Statements

Qualifying Statements

The recommendations contained in this guideline are a consensus of the Alberta Provincial Endocrine Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Implementation of the Guideline

Description of Implementation Strategy

- Present the guideline at the local and provincial tumour team meetings and weekly rounds
- Post the guideline on the Alberta Health Services Web site
- Send an electronic notification of the new guideline to all members of CancerControl Alberta

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

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tumours. Version 2. Edmonton (AB): CancerControl Alberta; 2015 Feb. 18 p. (Clinical practice guideline; no. ENDO-001). [68 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Nov (revised 2015 Feb)

Guideline Developer(s)

CancerControl Alberta - State/Local Government Agency [Non-U.S.]

Source(s) of Funding

CancerControl Alberta

Guideline Committee

Alberta Provincial Endocrine Tumour Team

Composition of Group That Authored the Guideline

Members of the Alberta Provincial Endocrine Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, dermatologists, nurses, pathologists, a pharmacist, methodologists, and Knowledge Management experts.

Financial Disclosures/Conflicts of Interest

Participation of members of the Alberta Provincial Endocrine Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Endocrine Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Alberta Health Services Web site.

Availability of Companion Documents

The following is available:

- Guideline utilization resource unit handbook. Version 2. Edmonton (Alberta): CancerControl Alberta; 2013 Jan. 5 p. Available from the Alberta Health Services Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on August 12, 2014. The information was verified by the guideline developer on September 25, 2014. This summary was updated by ECRI Institute on August 5, 2015. The updated information was verified by the guideline developer on October 22, 2015.

Copyright Statement

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